mmol) of pentynyltrimethylstannane (**28**). The yellow solution immediately turned black upon addition of the stannane. The reaction mixture was stirred for 30 min at 22-25 °C. Analysis by GLC (DB1, FID) indicated complete consumption of the vinyl iodide. The reaction mixture was transferred to a separatory funnel with 100 mL of ether and washed with 25 mL of water. The aqueous phase was diluted with 50 mL of water and back-extracted with 25 mL of ether. The combined ethereal extracts were washed with water (3 × 25 mL) and brine (1 × 25 mL) and dried over potassium carbonate. The solvents were removed under reduced pressure, and the remaining liquid was purified by radial chromatography by using hexane–ethyl acetate (8:2). Removal of the solvents provided 0.180 g (90.6%) of a pale yellow liquid: $^1$H NMR ($CDCl_3$) $\delta$ 0.94 (t, 3, $J$ = 7.4 Hz), 0.98–1.40 (m, 15), 1.50 (q, 2, $J$ = 7.2 Hz), 2.02 (q, 2, $J$ = 7.0 Hz), 2.21 (t, 2, $J$ = 6.9 Hz), 3.56 (t, 2, $J$ = 6.7 Hz), 5.40 (dt, 1, $J$ = 1.6, 15.8 Hz, CH=C*H*—C≡C), 6.00 (dt, 1, $J$ = 7.1, 15.8 Hz, C*H*=CH—C≡C); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.27, 21.32, 22.22, 25.70, 28.80, 28.96, 29.25, 29.31, 29.40, 32.76, 62.85, 79.44, 88.33, 110.02, 142.88, 146.61; IR (neat) 3350, 3025, 2920, 2860, 2215, 1055, 955 cm$^{-1}$. The $^1$H NMR and IR spectra matched the published data.[87]

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(87) Samain, D.; Descoins, C. *Bull. Soc. Chim. Fr.* **1979**, (*1-2, pt. 2*), 71.

# Methyl Transfers. 13. Transfers between Aryl Selenide Anions. An Unusual Transition State Charge Distribution[1]

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**Abstract:** The reaction rates and equilibria for the methylation of the phenyl selenide anion by aryl methyl selenides are reported. The reactions are much faster than the analogous reactions of thiophenoxide ion with aryl methyl sulfides. The Hammett equation is followed for the rates ($\rho^+ = +1.1 \pm 0.1$) and the equilibria ($\rho_{eq} = +2.9 \pm 0.1$) at 90 °C in sulfolane. The identity rate for phenyl can be interpolated, $k = (3.6 \pm 0.5) \times 10^{-4}$ s$^{-1}$ M$^{-1}$. The identity reactions have a derived $\rho_{xx} = -0.7$, and the charge on the methyl group in the transition state is −0.24. The significance of this unusual negative charge is discussed. The selenium compounds are all characterized by $^{77}$Se NMR, and the neutral selenides are fully characterized by $^{13}$C and $^1$H NMR as well.

Rates and equilibria of methyl transfers between nucleophiles differing only by a Hammett substituent can yield information on the charge distribution in the identity rate transition state **1**.[2] For the net negatively charged case shown, the charge on the

$$\left[\begin{matrix} -(1+\delta)/2 & \delta & -(1+\delta)/2 \\ X\text{-----}CH_3\text{-----}X \end{matrix}\right]^-$$

**1**

transition-state methyl groups, 5, is given by expression 1, in which $\rho^+$ refers to the Hammett $\rho$ for a variable leaving group.

$$\delta = 2(\rho^+/\rho_{eq}) - 1 \quad (1)$$

The ratio $\rho^+/\rho_{eq}$ is also given by the slope of a plot of log $k^+$ vs. log $K_{eq}$, which is a somewhat more general form if the Hammett equation fit is imperfect, or if the choice of $\sigma$ scales is not obvious. Such a plot can also be used for non-Hammett structural changes.[3] The substituent effect on the identity reaction, $\rho_{xx}$, is also derivable, and it is given by (2). In the earlier cases that we have studied,

$$\rho_{xx} = 2\rho^+ - \rho_{eq} \quad (2)$$

$\delta$ and $\rho_{xx}$ were positive,[2,4] and more or less equivalent statements are that the transition state has some carbocation character or that bond breaking is ahead of bond making. In these cases variation in the leaving group has more effect than variations in the attacking nucleophile on the reaction rate.[5]

Changes of a more drastic nature reveal little correlation of the identity rates with the equilibrium constant for methylating a standard nucleophile. Thus, methyl iodide hardly reacts at all with benzenesulfonate ion, yet its identity rate in sulfolane is more than $10^4$ times as fast as that of methyl benzenesulfonate.[4] We have been curious about the charge distribution in reactions of methyl iodide, but our technique of substituent effects cannot be used. In this paper we attempt to model iodide ion (and bromide ion) with nucleophiles capable of systematic substituent changes, but near in the periodic table. The obvious candidate would be substituted phenyl telluride anions. However, the chemistry of low oxidation state tellurium was not well developed, few of the compounds were known, and questions about toxicity and stench put us off.[6] Thus, we have compromised on the phenyl selenide anions and report here on reaction 3, getting both rate and

$$\text{ArSeMe} + \text{PhSe}^- \underset{k^-}{\overset{k^+}{\rightleftharpoons}} \text{ArSe}^- + \text{PhSeMe} \quad (K_{eq} = k^+/k^-) \quad (3)$$

equilibrium data, from which the identity rate of reaction 3 with Ar = Ph can be obtained by interpolation, and as described above the charge on the methyl group and the magnitude and direction of the substituent effect on the identity rate. The approach is closely analogous to that applied to the corresponding thiophenoxide anion case.[7]

## Results

The rates of reaction 3 were followed by determining the relative amounts of $ArSeCH_3$ and $PhSeCH_3$ from time to time initially with use of GC, but mostly HPLC. Equilibria were determined

(1) Paper 12: Lewis, E. S. *J. Phys. Chem.* **1986**, *90*, 3756. In part from the Ph.D. thesis of Thomas A. Douglas, Rice University, 1986. Work supported by a grant from the National Science Foundation.

(2) Lewis, E. S.; Hu, D. D. *J. Am. Chem. Soc.* **1984**, *106*, 3292.

(3) Kreevoy, M. M.; Lee, I.-S. H. *J. Am. Chem. Soc.* **1984**, *106*, 2550. This paper observes a slope less than $^1/_2$ and hence a negatively charged (hydride) transferring group.

(4) Lewis, E. S.; McLaughlin, M. L.; Douglas, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 6668.

(5) An interesting example is the following: Streitwieser, A. Jr. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 8288. Our positive $\delta$ corresponds to Streitwieser's case of $a > b$ in his eq 4.

(6) However, a recent review claims that the odors are not worse than the corresponding selenium compounds, and the tellurium compounds may be less toxic. The use of $PhTe^-$ is also reported. Engman, L. *Acc. Chem. Res.* **1985**, *18*, 274.

(7) Lewis, E. S.; Kukes, S. *J. Am. Chem. Soc.* **1979**, *101*, 417.

0002-7863/87/1509-2152$01.50/0 

Table I. Rate and Equilibrium Constants for Reaction 3

| X | $T$/°C | $k^+$[a]/$\times 10^{-4}$ $M^{-1}$ $s^{-1}$ | $K_{eq}$ |
|---|---|---|---|
| $NO_2$ | 90 | 21.1 ± 0.6 | |
| CN | 90 | 15.1 ± 0.3 | |
| $CF_3$ | 90 | 17.9 ± 0.5 | 69 ± 19 |
| Cl | 110 | 47.9 ± 0.7 | |
| Cl | 100 | 21.0 ± 0.5 | |
| Cl | 90 | 9.8 ± 0.6 | 8.5 ± 2.5 |
| Cl | 80 | 7.6[b] | |
| Cl | 70 | 3.7 ± 0.1 | |
| Cl | 60 | 2.24 ± 0.05 | |
| F | 90 | 4.29 ± 0.07 | 2.45 ± 0.35 |
| H | 90 | 3.52[c] | |
| Me | 120 | 18.5 ± 1.3 | |
| Me | 100 | 4.4 ± 0.3 | |
| Me | 90 | 2.4 ± 0.1 | 0.48 ± 0.22 |
| Me | 80 | 2.1[b] | |
| *t*-Bu | 90 | 2.27 ± 0.07 | 0.45 ± 0.15 |
| OMe | 90 | 1.28 ± 0.02[d] | 0.24 ± 0.06 |
| $NMe_2$ | 90 | 1.08 ± 0.03 | 0.029 ± 0.009 |

[a] Errors expressed at one standard deviation. [b] Obtained by GC analysis. [c] Interpolated in the log $k$–log $K$ plot, Figure 1. [d] Not believed to be as reliable as the standard deviation suggests because of less satisfactory analysis. Not used in calculating $\rho^+$ or the slope in Figure 1.

initially by GC and HPLC, but mostly by $^{77}$Se NMR.

Rates, when HPLC was used, were measured under *pseudo*-first-order conditions (cf. Experimental Section). This approach had the advantage both of making the rate constants independent of initial anion concentration and of suppressing the reverse reaction and thus simplifying the kinetic treatment. In the earlier GC work this was not the case, and the results are less precise for this reason. The rate and equilibrium constants are presented in Table I.

Phenyl selenide anion, the nucleophile in all our reactions, is rapidly air oxidized to the diselenide. Initially, it was used as the preformed[8] potassium salt. It is more convenient, however, to generate it in situ from reduction of diphenyl diselenide with excess (ca. 5:1) sodium borohydride.[9] Concern over the presence not of free selenide anion but of a borane complex[10] was heightened by the observation of an extra $^{77}$Se NMR peak at 74.2 ppm in a solution made by borohydride reduction in sulfolane and was confirmed by the observation of a broad peak at −14.4 ppm in the $^{11}$B spectrum, downfield of the $BH_4^-$ peak at −22.3 ppm (referenced to $BF_3$·$OEt_2$ as external standard). However, this extra peak disappeared irreversibly on heating to about 70 °C, leaving only a peak indistinguishable in chemical shift[11] from a solution of the diselenide reduced with 6% sodium amalgam in sulfolane. The lesser stability of the borane complex compared to Liotta's experience may be in part attributable to the solvent, but mostly to the concentration of selenide in solution, lower than his by about two orders of magnitude. The thermal destruction might be attributable to loss of diborane to the gas phase, or to destruction of diborane by the solvent or contaminants.[12]

Most of the measurements in Table I are reported at 90 °C, but runs for two compounds are shown over a wider range of temperatures. These lead for Ar = *p*-$ClC_6H_4$ to $\Delta H^\ddagger$ = 14.4 ± 1.1 kcal $mol^{-1}$, $\Delta S^\ddagger$ = −14.1 ± 0.9 cal $mol^{-1}$ $K^{-1}$ and for Ar = *p*-$CH_3C_6H_4$ to $\Delta H^\ddagger$ = 15.3 ± 2.8 kcal $mol^{-1}$, $\Delta S^\ddagger$ = −14.3 ± 2.3 cal $mol^{-1}$ $K^{-1}$.

Both the enthalpies and entropies of activation are the same for the two cases within experimental error (although the error is somewhat greater in the X = Me case); in this respect these reactions parallel those of the corresponding sulfides;[7] there are, however, two important differences: the entropies of activation for the selenide case are ca. 7 cal $mol^{-1}$ $K^{-1}$ *less* negative than for the sulfides, implying that phenyl selenide anions are somewhat less solvated in sulfolane than are phenyl sulfide anions in ethanol; and more strikingly, the activation enthalpies for the selenide cases are ca. 13 kcal $mol^{-1}$ lower than for the sulfide analogues ($\Delta H^\ddagger$ ~ 28 kcal $mol^{-1}$), reflecting the fact that aryl selenide ions are better nucleophiles (and leaving groups) than the corresponding sulfides.

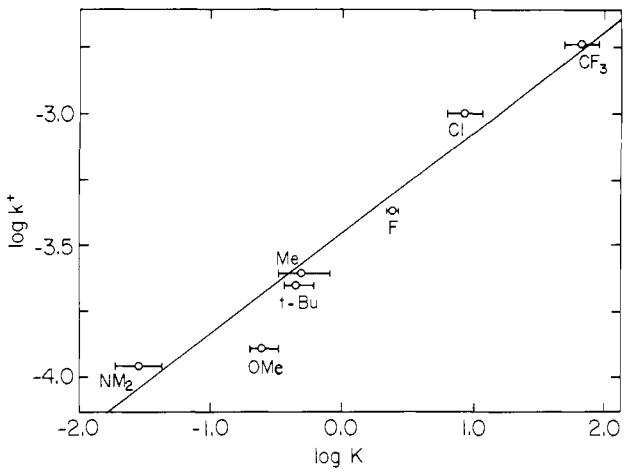


Figure 1. Rate vs. equilibrium plot of log $k^+$ vs. log $K$ for $PhSe^-$ + $CH_3SeAr \rightarrow PhSeCH_3 + {}^-SeAr$. The substituents on the aryl group are identified, and the slope is +0.38 ± 0.03. The rate constant for the *p*-$OCH_3$ case is not included in the plot; a different analysis was used, and the reliability is uncertain as described in the Experimental Section. The equilibrium constant in this case is as reliable as the others.

The $^{77}$Se NMR chemical shifts of the selenide anions, not previously reported in the literature,[13] are given in Table V. All the anions resonate upfield of the corresponding methyl phenyl selenides (as expected because of their negative charge) and are also more sensitive to substituent chemical shift; thus, in going from X = $CF_3$ to X = OMe there is a 112 ppm upfield shift in the anions (Table V), but in the corresponding methyl phenyl selenides the shift is only 24 ppm (Table V).

## Discussion

The rates and equilibria both fit the Hammett equation reasonably well, with $\rho^+$ = +1.1 ± 0.1 and $\rho_{eq}$ = +2.9 ± 0.1. The Hammett plots used $\sigma$ constants from benzoic acid ionization,[14] but the conclusions are not altered by a different choice of $\sigma$ values. This choice is, however, eliminated by using the LFER between the rate and the equilibrium constants. The plot of log $k^+$ vs. log $K_{eq}$ is shown in Figure 1. The slope of this plot is 0.38 ± 0.03, indistinguishable from the value derived from the Hammett plots, $\rho^+/\rho_{eq}$ = 0.38.

The slope of this plot is clearly significantly less than 0.5, in contrast to most earlier ones. Thus, the plot for transfer between arenesulfonate ions has a slope of 0.62,[2] and for transfers from aryl dimethyl selenonium ions[4] there is a slope of 0.55. The contrast is less for the transfer (in ethanol at high temperatures) between thiophenoxides,[6] a slope of 0.46, then believed to be indistinguishable from 0.5.

The slope less than 0.5 must correspond to a net negative charge (−0.24) on the transferring methyl group in the transition state.

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(11) Chemical shifts of the aryl selenide anions are quite sensitive to the presence of diselenide, presumably because of rapid exchange. Details of this process will be presented elsewhere.
(12) In this connection the $BH_3$ complex of $Me_2Se$ is extensively dissociated at room temperature: Graham, W. A. G.; Stone, F. G. A. *J. Inorg. Nucl. Chem.* **1956**, *3*, 164.
(13) McFarlane, H. C. E.; McFarlane, W. In *NMR of Newly Accessible Nuclei*; Laszlo, P., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 10.
(14) These were taken from Ritchie and Sager [Ritchie, C. D.; Sager, W. F. *Prog. Phys. Org. Chem.* **1964**, *2*, 323] except for the $\sigma$ value for the *p*-dimethylamino group, for which the benzoic acid $pK_a$ seems not to have been measured. The value chosen was that of Exner [Exner, O. In *Correlation Analysis in Chemistry: Recent Advances*; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1974]. Exner's $\sigma$ values for the other substituents are close to Ritchie and Sager's values.

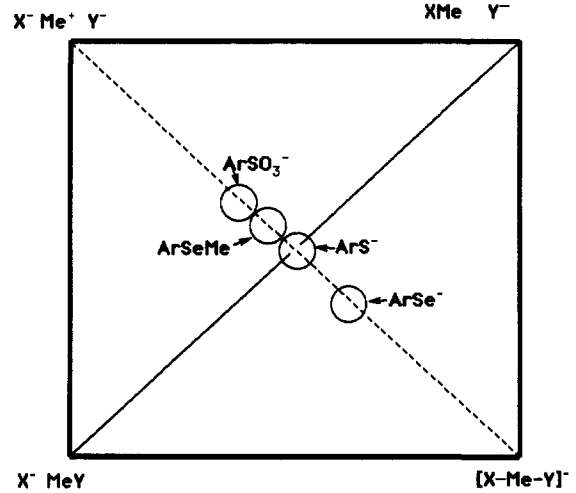


**Figure 2.** A More O'Ferrall–Jencks diagram, showing the location of the transition states for some identity reactions with respect to the symmetrical bonding to the central methyl, and the charge on this transferring group.

The More O'Ferrall–Jencks diagram of Figure 2 illustrates the charges on the transferring methyl group for these identity reactions. The structure in the lower left approached by this last case is uncertain. On the diagram it is shown as a hypervalent structure[15] with 10 shared electrons about carbon, giving it a formal charge of −1. Another structure, not violating the octet rule, is shown as **2**, in which the two odd electrons must be paired as a "formal bond".

$$\mathrm{PhSe^{\bullet}\quad \overset{-}{C}H_3\quad {}^{\bullet}SePh}$$
**2**

For appropriate symmetry, the methyl anion would have to have a planar structure. Still another description of this charge distribution can be offered. Since selenium is slightly less electronegative than carbon, there may be an extra negative change accumulation with two seleniums around carbon in the transition state. Contributions from any of these three sources are difficult to distinguish, and indeed there may not be a real difference.

However, according to Shaik,[16] identity reactions with first-row nucleophiles are loose or exploded with X–$CH_3$ transition state bonds far from the normal $CH_3X$ distance, whereas with iodide the "distortion effect" is much smaller, and the transition state is compact or tight. Although the language is quite different, our results have not been in conflict with Shaik's general conclusions.[17] Possibly the structure **2** is not in agreement with the tight transition state expected.

The positions of the identity reaction transition states in Figure 2 represent well the transition states for all methyl transfers, even of considerable asymmetry and exothermicity. That is, none of the spontaneous reactions have transition states that are significantly "reagent-like". This is shown by the lack of consistent "Reactivity–Selectivity Principle" (RSP) correlation,[18] and also by the demonstration that the contribution of the quadratic term in the Marcus equation (which appears to lead to the RSP) is small for all realistic methyl transfers.[19]

Even for non-identity reactions, the slopes of the log $k^+$ vs. log $K_{eq}$ plots differ from 0.5 almost entirely because of variation in intrinsic barrier. These slopes are not a measure of "progress along the reaction coordinate" or "product-like character".

The charge on the transferring methyl group may be extremely variable. Thus with a nucleophile like $PhSe^-$ (and possibly analogously $I^-$) attacking dimethyl sulfate the methyl group charge may be sort of an average between that characteristic of the $PhSe^-$ transfer identity reaction and that characteristic of the sulfonate leaving groups. This is consistent with the observation that the Marcus equation fits reasonably well the $I^- + Me_2SO_4$ reaction.[4] Conspicuous Marcus equation deviations, such as the much greater reactivity of $CH_3I$ than $(CH_3)_2SO_4$ with an iron nucleophile,[20] may reflect failures of such an averaging, otherwise describable as favorable "soft–soft" interactions.[21] Methyl iodide and dimethyl sulfate ordinarily have quite comparable reactivities, as described by their nearly identical $M_Y$ values.[22]

The complete characterization of these aryl methyl selenides as methylating agents requires equilibrium information that is not now available. Synthetic methods suggest that many methylating agents are more powerful than ArSeMe. Thus $PhSe^-$ dealkylates tertiary amines[23] and esters[10,24] and appears for many dealkylations to be more effective than $PhS^-$, which dealkylates alkyl aryl ethers.[25] We conclude that $PhSeCH_3$ is far down on the list in equilibrium methylating power.

Nevertheless, appropriately substituted selenium may be a significant leaving group. In a kinetic study of phenacyl transfers, $SeCN^-$, $SCN^-$, and $Br^-$ were equilibrated, and the equilibrium constants are not far from unity.[26] We hoped to be able to study nitrophenyl and cyanophenyl methyl selenides, and some rather rough rates are reported in Table I. These substituents are both reduced under our conditions for equilibration. The reducing agent might be excess borohydride, but it may also be the selenide anions, which are themselves good reducing agents. Although sodium borohydride is not generally able to reduce either nitro compounds or nitriles, the conventional reactivity may not apply in sulfolane at 90° for a day or so.

**Table II.** Synthesis and Physical Properties of 4-Substituted Methyl Aryl Selenides, *p*-$XC6H_4$-SeMe

| X | reaction employed | % yield | mp[a]/°C or bp/°C (mmHg) | appearance | lit. ref |
|---|---|---|---|---|---|
| $NO_2$ | diazotization | 18 | 57–57.5 | bright yellow cubes (from EtOH) | 4 |
| CN | diazotization | 18 | 57.5–58 | white prisms (from benzene) | 4 |
| $CF_3$ | Grignard | 67 | 32–33 | yellow needes (from $Et_2O$) | |
| Cl | Grignard | 58 | 26–28 | white needles (from $Et_2O$) | 4 |
| F | Grignard | 52 | 26–28 (0.03) | orange oil | 26 |
| H | Grignard | 54 | 36–38 (0.08) | colorless liquid | 4 |
| Me | Grignard | 60 | 32–34 (0.04) | pale yellow oil | 4 |
| *t*-Bu | Grignard | 33 | 58–60 (0.05) | red oil | |
| OMe | Grignard | 45 | 75–80 (0.1) | pale yellow oil | 4 |
| $NMe_2$ | Grignard | 48 | 28–30 (0.02) | colorless liquid | 26 |

[a] All melting points were determined on a FischerJohns melting points microscope and are uncorrected.

## Experimental Section

**Synthesis.** The 4-substituted aryl methyl selenides (Table II) were synthesized in low to moderate yields according to literature procedures[4,27] by either the Grignard reaction on the appropriate 4-substituted

(15) An analogous stable compound with sulfur instead of selenium has been isolated and presented as an $S_N2$ transition-state model. Martin, J. C. *Science* **1983**, *221*, 509.
(16) Shaik, S. S. *Isr. J. Chem.* **1985**, *26*, 357.
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(25) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, 1327. Kelly, T. R.; Edali, H. M.; Tsang, W.-G. *Tetrahedron Lett.* **1977**, 3859.
(26) Thorstenson, T.; Songstad, J. *Acta Chem. Scand. A* **1978**, *32*, 133.

**Table III.** $^1$H NMR Chemical Shifts[a] of 4-Substituted Methyl Aryl Selenides

| X | H(2,6)[b] | H(3,5)[b] | H(Me)[c] | H(X) |
|---|---|---|---|---|
| $NO_2$ | 8.13 | 7.50 | 2.50 | |
| CN | 7.52 | 7.45 | 2.48 | |
| $CF_3$ | 7.49 | 7.47[d] | 2.33 | |
| Cl | 7.41 | 7.29 | 2.41 | |
| F | 7.43[e] | 7.04[f] | 2.40 | |
| H | 7.53 | 7.35[g] | 2.45 | 7.29[g] |
| Me | 7.48 | 7.10 | 2.26 | 2.24 |
| *t*-Bu | *h* | *h* | 2.28 | 1.28 |
| OMe | 7.51 | 6.90 | 2.39 | 3.86 |
| $NMe_2$ | 7.52 | 7.46 | 2.36 | 2.48 |

[a] In ppm from $Me_4Si$ in $CDCl_3$. [b] All peaks are doublets with $^3J_{(H-H)}$ = (8.0 – 8.5) Hz unless otherwise stated. [c] $^2J_{(H-Se)}$ = 10–111 Hz. [d] Quartet: $^4J_{(H-F)}$ = 3.2 Hz. [e] Multiplet: $^3J_{(H-H)}$ = 8 Hz; $^4J_{(H-F)}$ = 4. Hz. [f] Tripet: $[^3J_{(H-F)} + {}^3J_{(H-H)}]/2$ = 8 Hz. [g] Triplet: $^3J_{(H-H)}$ = 8.4 Hz. [h] Multiplet at $\delta$ 7.30–7.44.

**Table IV.** $^{13}$C NMR Chemical Shifts[a] of 4-Substituted Methyl Aryl Selenides

| X | Cl | C(2,6) | C(3,5) | C4 | C(Me)[b] | C(X) |
|---|---|---|---|---|---|---|
| $NO_2$ | 143.2 | 128.7 | 123.7 | 145.8 | 6.6 | |
| CN | 108.8 | 129.0 | 131.9 | 140.0 | 6.3 | 118.6 |
| $CF_3$ | 139.5 | 126.6 | 130.1 | 127.9[c] | 6.7 | 126.6[d] |
| Cl | 130.1 | 131.8 | 129.1 | 132.2 | 7.5 | |
| F | 125.8[e] | 132.7[f] | 116.0[g] | 161.6[h] | 8.0 | |
| H | 131.8 | 129.0 | 130.4 | 126.1 | 7.1 | |
| Me | 127.9 | 130.9 | 129.7 | 135.9 | 7.5 | 20.8 |
| *t*-Bu | 129.1 | 130.7 | 126.9 | 150.1 | 7.3 | 31.6[i], 35.0[j] |
| OMe | 121.3 | 133.2 | 114.6 | 158.6 | 8.4 | 55.0 |
| $NMe_2$ | 117.9 | 135.2 | 114.0 | 150.8 | 8.6 | 40.4 |

[a] In ppm from $Me_4Si$ in $CDCl_3$ [b] $^1J_{(C-Se)}$ = 63–64 Hz. [c] Quartet: $^2J_{C-F}$ = 32.3 Hz. [d] Quartet: $^1J_{(C-F)}$ = 271 Hz. [e] Doublet: $^4J_{(C-F)}$ = 2.4 Hz. [f] Doublet: $^3J_{(C-F)}$ = 7.6 Hz. [g] Doublet: $^2J_{(C-F)}$ = 21.9 Hz. [h] Doublet: $^1J_{(C-F)}$ = 246.1 Hz. [i] Methyl carbon. [j] Quarternary carbon.

bromobenzene or diazotization of the appropriate 4-substituted aniline. All were purified by vacuum distillation followed by recrystallization (where appropriate); purity was >98.5% as shown by integration of their HPLC peaks and by their NMR spectra (vide infra).

**NMR.** All spectra were recorded at ambient probe temperatures on an IBM 300 spectrometer operating at 7.05 T. $CDCl_3$ was the solvent and internal lock for the $^1$H and $^{13}$C spectra; $^{77}$Se spectra were taken in sulfolane with either $CD_3OD$ or $CD_3CN$ as internal lock.

$^1$H NMR spectra were recorded at 300.13 MHz with a 10 $\mu$s (37°) pw with no pulse delay, but with a 5.11 s acquisition time; the spectral window was 3.2 kHz with 32K data points, giving a digital resolution of 0.2 Hz per point.

$^{13}$C NMR spectra were recorded fully decoupled at 75.46 MHz with a 1.5 $\mu$s (30°) pw with a 1.0 s pd and a 1.43 s acquisition time; the spectral window was 20 kHz with 32K data points, giving a digital resolution of 0.7 Hz per point.

$^{77}$Se spectra were recorded fully decoupled at 57.22 MHz with a 8.5 $\mu$s (90°) pw with a 3.0 s pd and a 0.9 s acquisition time; the spectral window was 29 kHz with 64K data points giving a digital resolution of 1.1 Hz per point.

The $^1$H, $^{13}$C, and $^{77}$Se chemical shifts are reported in Tables III, IV, and V, respectively. With the exception of X = CN, $CF_3$, and *t*-Bu, which have not been previously reported, all are in good agreement (within 0.1 ppm for $^1$H, 0.5 ppm for $^{13}$C, and 2 ppm for $^{77}$Se) with the literature values.[4,27]

**Kinetics.** Kinetic runs were carried out under Argon in stoppered 18 mm (o.d.) glass tubes suspended in a thermostated silicone oil bath. The temperature was maintained at 90.0 ± 0.1 °C (unless otherwise stated) by using a Bayley Instruments Precision Temperature Controller 253 and was checked periodically with an NBS thermometer calibrated to 0.1 °C.

Reactions were started by the addition of excess $NaBH_4$ (from a spatula) to a thermostated solution of diphenyl diselenide (Aldrich) and the appropriate methyl aryl selenide in purified[17] sulfolane. Solutions were typically prepared in 5 or 10 mL volumetric flasks. The initial concentrations were typically 0.5 M (methyl aryl selenide) and $5 \times 10^{-3}$ M diphenyl diselenide; thus the excess of methylating agent over nucleophile was ca. 50:1, ensuring pseudo-first-order kinetics. The addition

(27) Kahabin, G. A.; Kushrarev, D. F.; Bzesovsky, V. M.; Tschmutova, G. A. *Org. Magn. Reson.* **1979**, *12*, No. 10, 598.

**Table V.** $^{77}$Se NMR Chemical Shifts[a] of 4-Substituted Aryl Methyl Selenides and 4-Substituted Aryl Selenide Anions

| X | $XC_6H_4SeMe$ | $XC_6H_4Se^-$ |
|---|---|---|
| $NO_2$ | 236.0 | *b* |
| CN | 230.2 | *b* |
| $CF_3$ | 215.8 | 206.2 |
| Cl | 205.0 | 159.2 |
| F | 200.7 | 149.5 |
| H | 202.0 | 140.4 |
| Me | 194.8 | 114.6 |
| *t*-Bu | 195.1 | 102.0 |
| OMe | 191.6 | 93.9 |
| $NMe_2$ | 184.0 | *b* |

[a] In sulfolane referenced to external, neat $Me_2Se$. [b] Not observed.

of $NaBH_4$ resulted in immediate loss of color due to conversion of the bright yellow diselenide to the colorless phenyl selenide anion and was accompanied by the vigorous effervescence of hydrogen. All solutions remained colorless throughout the course of the reactions, with the exceptions of X = CN, $NO_2$ which became bright green and intensely purple, respectively, within a few minutes of $t$ = 0. These colors could be due to the formation of the highly conjugated product aryl selenide anions or to anionic radical intermediates formed in the reduction of the substituent by SET from phenyl selenide anion. However, no ESR signal was observed in these solutions. Reduction does occur; see the subsection Equilibria below.

Samples (ca. 0.1 mL) were removed for analysis with use of a 0.25 mL syringe at intervals ranging from a few minutes for the very fast reactions (e.g., with X = $NO_2$, CN) to ca. 1 h for the very slow reactions (e.g., X = $NMe_2$). Similarly, $t_\infty$ values were taken as early as a few hours and as late as 4 days. All $t_\infty$ values were taken in triplicate, and reaction was deemed to have gone to completion (>7 half-lives) when two successive values were the same to two significant figures. All samples were analyzed by HPLC on a Kontron 414LC pump with a Valco C6W manual injection valve and a Spectroflow 757 UV detector operating at 250 nm. With the singular exception of X = OMe, all reaction mixtures were followed in reverse phase by using a 25 cm custom LC C18 ODS column and acetonitrile:water, 2:1 (v/v), as the mobile phase. This solvent was also used to dilute samples prior to injection. Typical operating parameters were the following: flow rate = 2 mL min$^{-1}$; pressure = 2000 psi; injection volume = (2–5) $\mu$L; retention time = 2.5 min (for PhSeMe). All the 4-substituted aryl methyl selenides, with the exception of X = CN, $NO_2$, had retention times longer than PhSeMe. The latter two are eluted before PhSeMe, presumably because they have highly polar substituents which favor partitioning into the polar mobile phase.

For X = OMe, the samples were diluted with water (ca. 1 mL) and the organic components extracted into *n*-hexane. The hexane solutions were then analyzed on a 15-cm Custom LC silica (3 $\mu$m) column with *n*-hexane as the mobile phase. Typical operating parameters were the following: flow rate = 1.3 mL min$^{-1}$; pressure = 500 psi; injection volume = 20 $\mu$L; retention time = 1.8 min (for PhSeMe). Under these conditions the retention time of 4-methoxyphenyl methyl selenide is prohibitively long. The flow rate was therefore raised to ca. 4 mL min$^{-1}$ upon elution of the PhSeMe peak, and the second peak subsequently appeared within ca. 2 min. The rate constant does not appear reliable; it deviated from both the Hammett plot and the line in Figure 1.

Peak areas were calculated with use of an HP 3390A integrator. Pseudo-first-order rate constants were obtained from the slope of an unweighted linear least squares plot of (4). The ArSeMe peak was used as internal standard, as the concentration of ArSeMe remains constant

$$\ln\left[\frac{\text{area(PhSeMe)}_\infty}{\text{area(ArSeMe)}_\infty} - \frac{\text{area(PhSeMe)}_t}{\text{area(ArSeMe)}_t}\right] \text{ vs. time} \qquad (4)$$

throughout the run (to within ca. 2% error). Reactions were followed to ca. 70–80% completion and typically 6–8 points were used in each rate plot. Second-order rate constants were obtained from the following relationship: $k_2 = k_{obsd}/[\text{ArSeMe}]_0$. In one case, X = Me, the reaction was repeated at a different initial concentration of ArSeMe. The resultant value, $k_2 = (2.31 \pm 0.05) \times 10^{-4}$, is identical, within experimental error, with that given in Table I.

**Equilibria.** All equilibrium constants were obtained from $^{77}$Se NMR spectra of mixtures in sealed 10-mm NMR tubes. Reactions were started in precisely the same manner as with the rate studies (vide supra) except that initial concentrations of both reactants were comparable at ca. 0.05–0.10 M. Time taken to achieve equilibrium varied from a few hours (X = $CF_3$) to ca. 1 week (X = $NMe_2$). For X = $NO_2$ and CN, the $^{77}$Se NMR spectra revealed the complete disappearance of starting material (ArSeMe) and the appearance of a strong peak at 183.5 and 194.8 ppm

for $NO_2$ and CN, respectively, together with product, PhSeMe. The former peak was identified as 4-aminophenyl methyl selenide (lit.[27] 182.0 ppm) and the latter tentatively assigned to 4-aminomethylphenyl methyl selenide by using the $\sigma$ value of aminomethyl (-0.22)[12] and the following equation:[27] $\delta(^{77}Se) = 202.6 + 32.5\sigma$ (calcd 199.0 ppm; found 194.8 ppm). Clearly these products are formed from the reduction of the substituents, a phenomenon that has previously been observed with thiophenoxide[28] and may cause the intense color of these solutions as noted above.

This competing reduction of starting material by $PhSe^-$ was of less significance in the rate studies because reaction times were of the order of a few minutes, due to the excess of methyl aryl selenide.

For X = $NMe_2$, where the equilibrium constant is far from unity, the product anion was not observed. The equilibrium constant was therefore obtained by using the following relationship: $K = x^2/(a - x)(b - x)$, where $a = [ArSeMe]_0$, $b = [PhSe^-Na^+]_0$, $x = ac/(1 + c)$, and $c$ is given by eq 5.

$$c = \frac{[PhSeMe]_e}{[ArSeMe]_e} = \frac{^{77}Se \text{ peak ht of PhSeMe at equilibrium}}{^{77}Se \text{ peak ht of ArSeMe at equilibrium}} \quad (5)$$

(28) Porter, H. K. *Org. React.* **1973**, *20*, 455.

For all the remaining substituents, equilibrium constants were obtained directly from the $^{77}Se$ NMR spectra by using the expression

$$K = \frac{[ArSe^-]_e[PhSeMe]_e}{[PhSe^-]_e[ArSeMe]_e} = \frac{(^{77}Se \text{ peak ht of } ArSe^-_{eq})(^{77}Se \text{ peak ht of } PhSeMe_{eq})}{(^{77}Se \text{ peak hut of } PhSe^-_{eq})(^{77}Se \text{ peak ht of } ArSeMe_{eq})} \quad (6)$$

In all cases, errors in peak heights were obtained from the root mean square noise and these in turn were used to calculate the error in $K$. In one case, X = Me, the equilibrium mixture was analyzed by HPLC (using pre-prepared volumetric solutions to correct for the different extinction coefficient of ArSeMe and PhSeMe at 250 nm) and the mean value obtained: $K = 0.37$ is in excellent agreement with that given in Table I. In another example, X = Cl and F, the values were checked for internal consistency by determining the equilibrium constant between 4-fluorophenyl methyl selenide and the sodium salt of 4-chlorophenyl selenide (formed in situ from bis(*p*-chlorophenyl) diselenide). The value obtained, $K = 0.28$, is in breathtaking agreement with that obtained from Table I: $K(F)/K(Cl) = 2.45/8.5 = 0.29$.

For the X = $CF_3$ case, a similar relay procedure affords a value of $K(CF_3)/K(Cl) = 7.7$. Taking $K(Cl) = 8.5 \pm 2.5$ (Table I) affords a value of $K(CF_3) = 69 \pm 19$. This is the value quoted in Table I.

# The Mechanism for the Conversion of $\alpha$-Amino-$\beta$-carboxymuconate $\epsilon$-Semialdehyde to Quinolinate, an Apparent Nonenzymic Step in the Biosynthesis of the Nicotinamide Coenzymes from Tryptophan[1]

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**Abstract:** In the biosynthesis of the nicotinamide coenzymes from tryptophan in animals, apparently one step, namely, the conversion of $\alpha$-amino-$\beta$-carboxymuconate $\epsilon$-semialdehyde (**2**) to quinolinate (pyridine-2,3-dicarboxylate), proceeds by a nonenzyme-catalyzed reaction, even though it occurs at a branchpoint in typtophan metabolism. Because of its importance to mammalian metabolism, the mechanism of this nonenzymic reaction has been investigated and is reported here. In aqueous solution at 37 °C, quinolinate is the only product seen above pH 4.5, while below that pH a proton-catalyzed reaction forming $\alpha$-hydroxymuconate semialdehyde competes with quinolinate formation. The pH rate profile for quinolinate formation consists of a plateau rate (near pH 4.5) which titrates ($pK_a$ of **2** is 5.0) to a slower rate from ca. pH 7 to 11 and a hydroxide-catalyzed reaction at greater pH values. The reaction from pH 7 to 11 exhibits buffer catalysis and a change in rate-determining step. The zero buffer reaction occurs with a large solvent isotope effect ($k_{H_2O}/k_{D_2O} \geq 2.3$) and a secondary isotope effect ($k_D/k_H = 1.14$, D on aldehyde of **2**). Increasing the Tris buffer to 500 mM results in a loss of buffer catalysis, a loss of solvent deuterium isotope effect, and no change in secondary isotope effect. Catalysis by both the acidic and basic forms of the buffers is apparent. General acid catalysis is indicated by a Brønsted coefficient of $\alpha = 0.3$–$0.4$, and no catalytic advantage is seen with the catalysts dihydrogen phosphate and bicarbonate. These results indicate that carbinolamine dehydration is probably rate determining at low buffer concentrations while carbinolamine formation, probably by a pericyclic mechanism, is rate determining at high buffer concentrations. Under physiological conditions the reaction would be proceeding at a constant rate that would be insensitive to normal physiological fluctuations. Thus, control of this branchpoint in tryptophan metabolism is probably effected by control of the decarboxylase enzyme that competes with this nonenzymic step.

In animals, quinolinate (pyridine-2,3-dicarboxylate, **3**) and the nicotinate ring of the nicotinamide coenzymes are biosynthesized from tryptophan in a sequence of reactions outlined in abbreviated form in Scheme I.[2] That this is an important pathway in animal metabolism is evident from the observations that tryptophan can supply the entire niacin requirement for most animals[3] and that quinolinate is known to modify the activities of several important enzymes and biological processes.[4] Our interest in quinolinic acid biosynthesis arose from the observation that purified preparations

(1) (a) This work was supported by a research Grant (AM 13448) from the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, Public Health Service. (b) Taken from the Ph.D. Thesis of L.D.K., The Pennsylvania State University, 1983.

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